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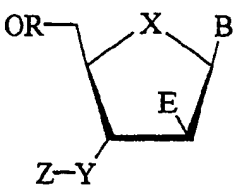
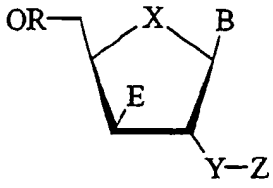
[Continued on next page]

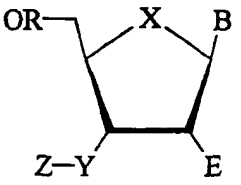
(54) Title: 3'-OR 2'-HYDROXYMETHYL SUBSTITUTED NUCLEOSIDE DERIVATIVES FOR TREATMENT OF HEPATITIS VIRUS INFECTIONS



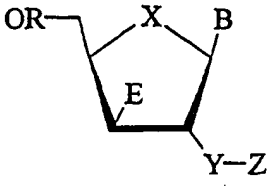
(I)



(III)



(II)



(IV)

(57) Abstract: The present invention relates to a composition for and a method of treating hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, hepatitis D virus (HDV) infection or a proliferative disorder in a patient using an effective amount of a compound selected from the group consisting of formulas (I)-(IV) below and mixtures of two or more thereof, wherein the substituents are as defined herein. Pharmaceutical compositions comprising these compounds in combination with other HBV, HCV, or HDV agents is also disclosed.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PC., US 01/12050

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/7068 A61K31/7072 A61K31/7076 A61K31/708 A61P31/12 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TSIBINOGIN, V. V. ET AL: "Inhibition of the replication of human hepatitis B virus" retrieved from STN Database accession no. 111:126519 XP002192805 See compounds having registry number: 90052-19-3 and 99614-95-6 & MOL. BIOL. (MOSCOW) (1989), 23(4), 983-7, --- -/--	17

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 March 2002	02 June 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MATTHES, ECKART ET AL: "Comparative inhibition of hepatitis B virus DNA polymerase and cellular DNA polymerases by triphosphates of sugar-modified 5-methyldeoxycytidines and of other nucleoside analogs" retrieved from STN Database accession no. 115:154849 XP002192806 See compound RN:109611-35-0 & ANTIMICROB. AGENTS CHEMOTHER. (1991), 35(6), 1254-7, ---	17
X	US 6 004 939 A (FLETCHER TERACE M ET AL) 21 December 1999 (1999-12-21) See column 53, "NA005" (Thymidine 5'-(trihydrogen diphosphate), 3'-amino-3'-deoxy-), RN= 233760-19-5) claims 1,5-16 column 18, line 53 -column 19, line 58 ---	17
X	VICTOROVA LYUBOV S ET AL: "Mode of inhibition of HIV reverse transcriptase-catalyzed DNA synthesis by 3'-amino-3'-deoxythymidine 5'-triphosphate." NUCLEOSIDES & NUCLEOTIDES, vol. 15, no. 1-3, 1996, pages 655-667, XP001062295 ISSN: 0732-8311 the whole document ---	17
Y	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; UEDA, TORU ET AL: "Preparation of 2'-deoxy-2'(S)-alkylpyrimidine nucleosides as antiviral agents" retrieved from STN Database accession no. 110:115271 CA XP002192807 See compound Registry Number : 119410-85-4 & JP 63 215694 A (YAMASA SHOYU CO., LTD., JAPAN) 8 September 1988 (1988-09-08) --- -/--	17

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MATSUDA, AKIRA ET AL: "Preparation of 2'-deoxy-(2'S)-alkylpyrimidine nucleosides as antiviral agents" retrieved from STN Database accession no. 122:31836 CA XP002192808 See compound having Registry Number: 159534-52-8 & JP 06 228186 A (YAMASA SHOYU KK, JAPAN) 16 August 1994 (1994-08-16) ---	17
Y	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MATTHES, E. ET AL: "Potent inhibition of hepatitis B virus production in vitro by modified pyrimidine nucleosides" retrieved from STN Database accession no. 114:17138 HCA XP002192809 See compound having Registry Number: 87190-81-6 & ANTIMICROB. AGENTS CHEMOTHER. (1990), 34(10), 1986-90, ---	17
A	MCGUIGAN C ET AL: "Alkyl Hydrogen Phosphonate Derivatives of the Anti-HIV Agent AZT may be Less Toxic than the Parent Nucleoside Analogue" ANTIVIRAL CHEMISTRY & CHEMOTHERAPY, BLACKWELL SCIENTIFIC PUBL., LONDON, GB, vol. 5, no. 4, 1994, pages 271-277, XP002105798 ISSN: 0956-3202 the whole document -----	17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/12050

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-16,23-25
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

17, (partial)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 17, (partial).

   Compositions comprising the phosphate derivatives falling in the definition of the Markush formulas I-IV in claim 17 (alone or in combination with other antiviral agents) and their use in relation to the treatment of hepatitis B (HBV).

2. Claim : Claims: 19 (partial).

   Compositions comprising the phosphate derivatives falling in the definition of the Markush formulas I-IV in claim 19 (alone or in combination with other antiviral agents) and their use in relation to the treatment of hepatitis C (HCV).

3. Claim : Claims: 21 (partial).

   Compositions comprising the phosphate derivatives falling in the definition of the Markush formulas I-IV in claim 21 (alone or in combination with other antiviral agents) and their use in relation to the treatment of hepatitis D (HDV).

4. Claims: Claims 17, 19, 21 (partial) (As far as not comprised in the previous inventions)

   Compositions comprising the acyl ($CH_3(CH_2)_nCO$-) derivatives falling in the definition of the Markush formulas I-IV in claims 1,17,19 21 (alone or in combination with other active agents) and their use in relation to the treatment of hepatitis and proliferative disorders.

5. Claims: Claims 17, 19, 21 (partial) (As far as not comprised in the previous inventions)

   Compositions comprising the aminoacyl ($R'(CH)NH_2CO$-) derivatives falling in the definition of the Markush formulas I-IV in claims 1,17,19 21 (alone or in combination with other active agents) and their use in relation to the treatment of hepatitis and proliferative disorders.

6. Claims: Claims 18, 20, 22 (partial)

   Compositions comprising the derivatives shown in claims 18, 20, 22 which are obtained from compounds of Markush formula

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

I to IV in claims 1,17,19 21, by remotion of the phosphate group; and their use in relation to the treatment of hepatitis and proliferative disorders.

7. Claims: Claims 23-24

Compositions comprising the phosphate derivatives falling in the definition of the Markush formulas I-IV in claims 1,17,19 21 (alone or in combination with other agents) and their use in relation to the treatment of proliferative diseases.

8. Claim : claim 25

Compositions comprising the derivatives shown in claims 18, 20, 22, 25 which are obtained from compounds of Markush formula I to IV in claims 1,17,19 21, by remotion of the phosphate group and their use in relation to the treatment of hepatitis and proliferative disorders.

9. Claims: claims 26-31

A process for the manufacture of the compounds having the formula shown in claim 26 comprising the steps indicated in claim 26-31

INTERNATIONAL SEARCH REPORT

'ormation on patent family members

International Application No
PC[redacted]US 01/12050

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6004939 A	21-12-1999	US 6054442 A	25-04-2000
		AU 6485996 A	05-02-1997
		WO 9702279 A1	23-01-1997
JP 63215694 A	08-09-1988	JP 1964621 C	25-08-1995
		JP 6099467 B	07-12-1994
JP 6228186 A	16-08-1994	NONE	